REMARKS

Claims 54, 56, 60-64, 66, 67, 69, 72, 73 and 76-86 are pending. The specification has been amended to correct certain typographical errors. The claims have been amended to claim certain aspects of the present invention.

Claims 54-76 were rejected under 35 USC 101 as being directed to naturally occurring polynucleotide sequences. This rejection is respectfully traversed, especially with respect to the present claims.

The rejection was improper previously because claims 64-69 specifically recite that the polynucleotide contains an artificial randomized linker between the V_H and the V_L domains. Such a linker does not occur in nature and certainly not in its orientation and location between these two domains. Claims 61-62 require the polynucleotide to contain both the V_H and the V_L domains linked together. Where is such a construct naturally found in nature since the light chain and the heavy chain are different genes?

The present claims recite either a polynucleotide having the unnatural linker or a polynucleotide having an animal tumor antigen with a plant or a plant virus expression sequences. None of these constructions occurs naturally.

Claims 54-76 were rejected under 35 USC 112, second paragraph as being indefinite. The word "about" was considered vague in claims 66 and 76. This rejection is respectfully traversed.

No basis for the rejection of claims 54-65 and 70-75 was given and therefore such claims apparently meet the standards of 112, second paragraph. As for claim 66, the word "about" is definite within the meaning of 112 because the linker is a randomized one and the exact length is variable by the randomization process. The number of polynucleotides in the linker denotes a range of linker lengths. The invention is still a polynucleotide encoding the polypeptide having certain properties and the linker is still a linker that performs its linking function and maintains the remaining properties of both the polynucleotide and the polypeptide. This term "about" is understood by those skilled in the art within the context of the present usage.

As for claim 76, the language "at least about 15 μg" is a large range with no upper limit and a lower limit of about 15 μg. As for the Examiner's examples of 15 mg and 50 mg, both of these are quite high, ~1000 fold above the minimum, but technically fall within the range claimed. As for the timing of the injections, claim 76 was amended to clarify the timing of the injections. As

the examiner is well aware, the exact timing of the immunizations is not important and general principles for immunization schedules are well known.

Claims 54-74 were rejected under 35 USC 112, first paragraph as to enablement of the full scope of the claims. This rejection is respectfully traversed.

The claims have been amended extensively without prejudice for reasons other than this improper rejection based solely on the examiner's speculation. Nonetheless, the present claims coincidentally avoid most if not all of the Examiner's objections. The examiner's comments regarding determining not being able to determine individuals at risk of developing a tumor are surprising because the examiner has missed a primary usage for the present vaccine described in the specification. Individuals who are presently in remission for a particular cancer are at very high risk for the same cancer reoccurring and would be an ideal population for vaccination along with present cancer patients.

The examiner's speculation that tumor vaccines have not been shown to be effective is clearly wrong as many publications and even issued U.S. patents claim the contrary. While these tumor vaccines are not perfect, their success rate is vastly above background in the patient population tested. The examiner relies on Evans et al to stating that cancer vaccines are not sufficiently perfected to replace standard therapeutic strategies. Since "standard therapeutic strategies" frequently fail, as shown by cancer being the second most common cause of death in the U.S., perfection of tumor vaccines need not be accomplished for them to be useful in conjunction with standard therapies or when standard therapies are usually ineffective. Recent published clinical results have been very promising; three from December 2002 are attached as Exhibit A. All three abstracts are the work of the assignee and none are prior art.

Claims 54, 57-66, 70, 72, 73 and 75 were rejected under 35 USC 102(b) as being anticipated by Casper et al. These claims have been amended and with respect to the present claims, this rejection is clearly not appropriate for a number of reasons, the most apparent is that Casper produces their protein vaccines in insect cells or mammalian cells, not plant cells. Applicants submit that plants are very different from animals. Furthermore, contrary to the office action on page 8, last three lines, Casper et al mentions only one linker, $(Gly_3Ser_1)_4$. The taught linker is not within the claims and a randomized linker is not taught.

As for original claim 54, Casper et al does not show feature (d), the last paragraph stating that it "is capable of inducing an immune response...without a need for adjuvant or other

immunostimulatory materials..." The immunizations of scFv polypeptide in Casper et al include murine GM-CSF. Therefore, Casper et al does not teach every feature recited in claim 54 and by inference its dependant claims as well. Accordingly, the rejection should be withdrawn.

Claims 54-67, 70, 72, 73 and 75 were rejected under 35 USC 103(a) as being unpatentable over Casper et al in view of McCormick et al. This rejection is respectfully traversed.

McCormick et al is not prior art, being published less than one year before the filing date of the earliest application from which the present application claims priority to. Attached as Exhibit B is a photocopy of a declaration demonstrating that not all of the authors of McCormick et al are inventors rendering McCormick et al ineffective as a reference against the claims of the present application. The original declaration was filed in U.S. Serial number 09/522,900, filed March 10, 2000. Without the McCormick et al reference, no additional information is added to the Casper et al reference and thus the rejection is moot and the Caspar et al reference is deficient alone for the reasons above and therefore this rejection should be withdrawn for the same reasons.

Claims 54, 57-67, 70, 72, 73 and 75-76 were rejected under 35 USC 103(a) as being unpatentable over Casper et al in view of King et al. This rejection is respectfully traversed.

The King et al reference was cited as disclosing administering 15 μg of scFv subcutaneously about two weeks apart. Actually, King et al disclose vaccination with 50 μg of scFv subcutaneously on days 0, 21 and 28 or three weeks and one week apart respectively. See page 1285, second column, third full paragraph entitled "Vaccination and tumor challenge.", third sentence.

The rejection also states on page 11, lines 5-8, "One of ordinary skill in the art would have been motivated to administer the scFv polypeptide encoded for by a ploynucleotide because King et al taught the method of administration and provided dosage and administration intervals..." This allegation is contraindicated by the King et al reference itself. When King et al administered their scFv polypeptide, **ALL** of the mice died in 30 days when challenged by the tumor. See the data in Figure 7 on page 1285. The only mice that survived were inoculated with DNA fusion nucleic acid with fragment C of tetanus toxin. Again, see Figure 7 on page 1285. Accordingly, King et al specifically teaches away from using their scFv polypeptide vaccine.

With King et al teaching away from anything close to the present invention, Caspar et al again stands alone and therefore this rejection should be withdrawn for the same reasons.

Applicants note that claims 68, 69, 71 and 74 were not rejected over prior art.

CONCLUSIONS

In view of the amendments and comments above, the rejections have been overcome. Reconsideration, withdrawal of the rejections and early indication of allowance of claims 54, 56, 60-64, 66, 67, 69, 72, 73 and 76-86 are respectfully requested.

The commissioner hereby is authorized to charge payment of any fees under 37 CFR § 1.17, which may become due in connection with the instant application or credit any overpayment to Deposit Account No. 500933.

Respectfully submitted,

John E. Tarcza
Reg. No. 33,638

Enclosures:
Exhibit A: 3 abstracts
Exhibit B: photocopy of Declaration

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I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an enveloped addressed to:
Assistant Commissioner for Patents
Washington, DC 20231

On March 31, 2002

Typed or printed name of person signing this certificate John E. Tarcza

Signature

Marked up copy of claims as amended

54. (amended) A polynucleotide encoding a polypeptide [self-] epitope of a B-cell lymphoma surface immunoglobulin antigen useful as a tumor-specific vaccine in a subject with a tumor or at risk of developing a tumor, encoded at least in part by a nucleic acid in the cells of said tumor, and a nucleic acid sequence promoting expression of said polypeptide in a plant cell or plant, which polypeptide:

(a) includes an epitope or epitopes unique to, or overexpressed by, cells of said tumor, thereby distinguishing said tumor from all other tumors (i) of the same or different histological type, (ii) in said subject or in another member of said subject' s species;

(b) is produced in a plant cell or plant [organism] that has been transformed or transfected with said nucleic acid derived from said tumor of said subject;

(c) is obtainable from said plant cell or plant [organism] in correctly folded form, without a need for denaturation and renaturation and mimics said epitope or epitopes in their native form; and

(d) is capable of inducing an immune response in a mammal, including said subject, [without a need for adjuvant or other immunostimulatory materials] so that administration of said polypeptide results in an antibody or cell-mediated immune response to said epitope or epitopes.

56. (amended) The polynucleotide of claim [55] 54 wherein said polypeptide is produced transiently in said transformed or transfected plant.

60. (amended) The polynucleotide of claim [59] 54 said polypeptide [further] comprising two V region domains of said immunoglobulin.

66. (amended) The polynucleotide of claim [65] 64 wherein said domains of said polypeptides are linked by an amino acid linker that

(a) has between one and about 50 residues;
(b) consists of between one and 12 different amino acids, and
(c) facilitates secretion and correct folding of said polypeptide to mimic the tumor epitope in its native form in or on said tumor cell.

69. (amended) The polynucleotide of claim [67] 66, wherein in said linker of said polypeptide,

(i) position 1 of each repeated triplet is deoxyadenosine or deoxyguanosine;
(ii) position 2 of each repeated triplet is deoxycytidine or deoxyguanosine; and
(iii) position 3 of each repeated triplet is deoxythymidine.

76. (amended) The polynucleotide of claim 73, wherein said administration comprises subcutaneous immunization with at least about 15μg of said polypeptide antigen three times each about two weeks apart.

Exhibit A

Abstracts from the American Society of Hematology
44th annual meeting December 2002

[609] Plant Derived Single-Chain Fv Idiotype Vaccines Are Safe and Immunogenic in Patients with Follicular Lymphoma: Results of a Phase I Study.

Sunil A. Reddy, Debbie Czerwinski, Ranjana Rajapaksa, Steve Reinl, Steve J. Garger, Terry Cameron, Julia Barrett, Jeanne Novak, R. Barry Holtz, Ronald Levy. Division of Oncology, Stanford Medical Center, Stanford, CA, USA; Large Scale Biology, Vacaville, CA, USA; Colorado Bioregistry; Evergreen, CO, USA

Idiotype vaccines for follicular B cell lymphoma are currently in phase III trials. However, the optimal vaccine formulation is still unknown. Novel strategies will continue to be explored in order to improve upon current protein vaccines. Areas in which improvements would be welcome include increasing the speed of vaccine production and maximizing immunogenicity. Towards this end, we have explored the use of idiotype vaccines produced in plants. This is the first report of the testing of a recombinant virus expressed, plant derived, autologous vaccine in humans. In this trial, single-chain Fv (scFv) idiotype protein vaccine was produced in the plant *Nicotiana benthamiana*, utilizing recombinant technology. The purpose of this phase I study was to explore the feasibility of scFv vaccine production, safety of vaccination, and measurement of immune responses in patients with follicular lymphoma who were in first chemotherapy induced remission. 16 patients were assigned to one of four treatment groups:

Table 1

	scFv Vaccine	scFv Vaccine + GM-CSF
Low Dose (0.2mg)	Group 1 (n=4)	Group 3 (n=4)
High Dose (2.0mg)	Group 2 (n=4)	Group 4 (n=4)

A total of six monthly treatments were planned for each patient. 15 of 16 planned patients have completed vaccination, with one patient showing progression of lymphoma before completion of the vaccine series. There were no significant toxicities or serious adverse events reported during the course of vaccine administration. 10 of 16 patients have developed immune responses to the vaccine. Both humoral and cellular responses were observed. Six patients developed specific cellular immune responses after vaccination: 4/8 in the GM-CSF arms (groups 3,4) versus 2/8 in the non GM-CSF arms (Groups 1,2). One group 4 patient received only 1 of 6 planned rounds of GM-CSF and did not make an immune response. There was no obvious advantage of the high dose (2.0 mg) as compared to the low dose (0.2mg) of vaccine. In conclusion, plant derived scFv idiotype vaccines are feasible to produce, safe to administer and can generate idiotype-specific immune responses. In contrast to previous vaccine formulations, no KLH conjugation was used in this study. A Phase II study utilizing an expanded cohort of patients with follicular lymphoma is planned.

Keywords: Follicular lymphoma\ Idiotype vaccines\ Single-chain Fv

Abstracts from the American Society of Hematology
44th annual meeting December 2002

[2274] Enhanced In Vivo Response to an Idiotype Lymphoma Vaccine.
Alison McCormick, Terri Cameron, Fakhrieh Vojdani, Daniel Tuse. Large Scale Biology Corporation, Vacaville, CA, USA

B-cell lymphoma idiotype vaccines, where the tumor antigen is the surface Ig of the malignant B-cell clone, typically generate weak immune responses and often fail to induce protective immunity when administered singly as soluble proteins (Campbell et al., 1990, J. Immunol 145, 1029). Poor immunogenicity has been partially addressed by coupling the Ig to Keyhole Lympet Hemocyanin (KLH), a strongly immunogenic carrier. This technique has proven effective in both preclinical and human clinical trials (Hsu, et al., 1997, Blood 89, 3129; Bendandi et al., 1999, Nat Med 5, 171; Timmerman and Levy, 2000, J. Immunol 164, 4797). Another contributor to the poor immunogenicity of Ig idiotype vaccines may be related to the autologous constant region of the antibody, because immune tolerance can be partially overcome by grafting xenogeneic constant regions (Syrengelyas et al., 1996, Nature Med 9, 1038). We have studied a combination approach, removing the constant region completely and expressing only the tumor idiotype gene sequences as single-chain Fv (scFv) proteins using a plant virus-based transient expression vector in Nicotiana benthamiana host plants, and have evaluated the immunogenicity of these proteins with and without KLH conjugation. Previously we reported that strong protective immunity (80%) could be obtained when 15 mcg of 38C13 scFv protein was administered three times without adjuvant (McCormick et al, 1999, PNAS 96, 703). Here we report the results of a similar study using suboptimal doses of the vaccine, with or without KLH, using the 38C13 murine lymphoma model. Vaccinating twice with 1.5 mcg protein (1/10th the previously reported dosage used in multiple immunizations) coupled to KLH induced rapid and protective immune titers statistically similar to 38C13 Ig-KLH, with an overall survival rate of 70%. In a parallel experiment, a single dose of 15 mcg of the scFv-KLH conjugate gave significant survival (40%) compared to the Ig-KLH conjugate (50%), whereas at this dose the nonconjugated scFv protein failed to protect mice from lethal tumor challenge. In both experiments, high levels of IgG2 antibodies were measured in the sera of vaccinated mice. Our data suggest that Ig subunit vaccines can elicit superior immunogenicity and improved survival by removal of constant region and/or coupling to KLH for administration without adjuvant.
Keywords: Idiotype vaccine\ Plant scFv\ KLH conjugation

Abstracts from the American Society of Hematology
44th annual meeting December 2002

[2994] Immune Cell Proteome: Proteomic Analysis towards the Identification of New Biomarkers for Hematopoietic Malignancies.

Thomas A. Davis, Sharon L. Wannberg, Anthony Makusky, Jeff Zhou, Tina Gatlin, Daniel Tuse. Immunology and Stem Cell Biology Program and Proteomics Department, Large Scale Biology Corporation, Germantown, MD, USA

Proteomics can be a valuable tool in the identification of proteins and biochemical pathways involved in hematopoietic malignancies. Protein-level profiling uniquely allows delineation of global changes in protein expression patterns resulting from transcriptional control, post-translational modifications, and redistribution of protein pools among cellular compartments. We developed and applied a variety of techniques, including cell type-specific immunoselection, rigorous sample processing, two-dimensional electrophoresis, mass spectrometry, and comprehensive data analysis, imaging and mining, with the goal of elucidating proteins and pathways deregulated in B-cell non-Hodgkin's lymphoma (NHL). Peripheral blood immune cells, platelets and malignant B-cells from lymph nodes of NHL patients were purified using positive immunomagnetic selection. Using 2-dimensional gel analysis, protein profile master patterns were generated for cytoplasmic and nuclear proteins. We successfully identified lineage-specific proteins and mapped differences in protein expression between peripheral blood WBC, mononuclear cells, neutrophils, monocytes, $CD19^+$ B cells, $CD4^+$ T cells, $CD8^+$ T cells, $CD83^+$ dendritic cells, platelets and lambda light chain-positive lymph node NHL B cells. Our techniques allowed the clear visualization of protein signals specific to malignant B cells (NHL tumor), manifested either as new, overexpressed or underexpressed relative to normal $CD19^+$ B-cell controls. Larger clinical sample sets, currently under quantitative analysis, may reveal whether these changes in protein profiles represent disease-specific markers. These findings from our large-scale protein discovery program may facilitate the development of novel classification schemes for staging of immune and hematopoietic cell disorders, the identification of novel markers for early diagnosis of malignant diseases, and the elucidation of prognostic indicators with clinical utility.
Keywords: Immune cell proteome\ Proteomics\ Non Hodgkins lymphoma

Exhibit B

42200 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	:	
Alison A. McCormick et al.	:	Art Unit: 1642
Serial No. 09/522,900	:	Examiner: Geetha Bansal
Filed: 10 March 2000	:	
For: Self Antigen Vaccines for Treating B Cell Lymphomas And Other Cancers	:	

DECLARATION

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

We, the undersigned do hereby declare and state:

(1) We are the inventors of the above-captioned application, as evidenced by the Declaration previously filed and the Substitute Declaration attached hereto.

(2) Some of us are co-authors of the McCormick et al., Proceedings of the National Academy of Sciences, article appearing in Volume 96 at pages 703-308.

(3) Monto Kumagai, Kathleen Hanley, Itzhak Hakim, Laurence Grill, Shoshana Levy and Ronald Levy either worked under our direction or provided starting materials.

(4) Monto Kumagai, Kathleen Hanley, Itzhak Hakim, Laurence Grill, Shoshana Levy and Ronald Levy are not inventors of the subject matter disclosed in the instant application.

DECLARATION
Serial No. 09/522,900

The undersigned declare further that all statements made herein of their own knowledge are true and that all statements made on information and belief are believed to be true; and further that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Further Declarants sayeth not.

5-13-02
Date

Alison McCormick

5-13-02
Date

Daniel Tuse

5-14-02
Date

Stephen J. Reinl

5/14/02
Date

John A. Lindbo

5/10/02
Date

Thomas H. Turpen